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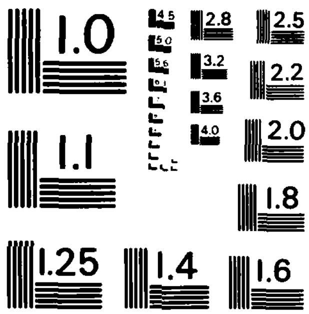

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MAXIMUM LIKELIHOOD ESTIMATION OF THE SURVIVAL FUNCTIONS

OF N STOCHASTICALLY ORDERED RANDOM VARIABLES

by

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ABSTRACT

Very often, populations exist that, logically, should satisfy linear stochastic ordering requirements. For example if a mechanical device is improved through N stages, the corresponding survival functions should be linearly stochastically ordered. Nevertheless, estimates may not reflect this stochastic ordering because of the inherent variability of the observations.

~~Here we~~ characterizes the maximum likelihood estimates of the survival functions subject to linear stochastic ordering requirements. These ~~We show our~~ estimates may be expressed in terms of the well-known Kaplan-Meier product limit estimates. ~~We~~ also is given an iterative algorithm which we show must converge to the correct solution that depends only upon solving the pairwise problem.

Finally ~~we~~ consider an example concerning survival times for people with squamous carcinoma in the oropharynx when classified by degree of lymph node deterioration at time of discovery.

Key Words and Phrases: Maximum likelihood estimation; survival functions; linear stochastic ordering; censored data; Kaplan-Meier product limit estimator; order restrictions; Kuhn-Tucker vectors.

AMS Classification Numbers: Primary 60G05; Secondary 62N05.

1. INTRODUCTION.

Often one wishes to estimate the survival functions (1-cumulative distribution function) of populations from possibly censored data when nothing is known concerning the functional form of the survival functions. Appealing estimates in this situation have been obtained by Kaplan and Meier (1958) and are usually referred to as Kaplan-Meier product limit estimators. Although Kaplan and Meier restricted themselves to discrete distributions, Johansen (1978) has shown that the product limit estimator is a maximum likelihood estimator (mle) in the class of all distributions under the generalized maximum likelihood framework developed by Kiefer and Wolfowitz (1956).

Many times one may have a situation where, logically, distributions must be stochastically ordered. For example, if a mechanical device is improved, the probability of survival past any given time for the improved device should not be less than that for the original device. In this situation, it seems reasonable to require that estimates of the survival functions should also satisfy this stochastic ordering. Brunk et al. (1966) have given mle's for two stochastically ordered cdf's for uncensored independent random samples. Dykstra (1982) has considered this problem for the case of right censored data and has given the mle's in the form of Kaplan-Meier product limit estimators with modified data. In this paper, we are able to find the mle's of $N \geq 2$ survival functions when a linear stochastic ordering exists among them. While the solution has a nice characterization, obtaining the actual estimates is quite difficult. An iterative algorithm depending only upon the solution to the pairwise problem is given and is shown to converge to an actual mle.

2. THE PROBLEM

We shall assume that we have independent random samples, possibly with right censored observations, from N discrete populations. The $N \geq 2$ populations are assumed to be stochastically ordered, so that the corresponding survival functions satisfy

$$P_1 \overset{st}{\geq} P_2 \overset{st}{\geq} \cdots \overset{st}{\geq} P_N. \tag{2.1}$$

(We say $P_i \overset{st}{\geq} P_j$ if $P_i(t) \geq P_j(t)$ for all t.) The problem is to find nonparametric mle's of the survival functions subject to the constraints in (2.1). We will without loss of generality (WLOG) assume that $P_1(0) = P_2(0) = \cdots = P_N(0) = 1$, so that all observations are positive.

Complete observations (failures) occur on a subset of the times $S_1 < S_2 < \cdots < S_m$ $(S_0 = 0, S_{m+1} = \infty)$. The number of failures from the i^{th} population which occur at time S_j is denoted by d_{ij}. The number of losses (censored observations) in the interval $[S_j, S_{j+1})$ from the i^{th} population is denoted by ℓ_{ij}. We assume the ℓ_{ij} losses occur at times $L_r^{(ij)}$, $r = 1, \cdots, \ell_{ij}$, where these censoring times are fixed. (The same mle's would obtain for random censoring times which are independent of the times of failure.) Let $n_{ij} = \sum_{r=j}^{m} (d_{ir} + \ell_{ir})$ denote the number of items from the i^{th} population surviving to just prior to S_j. We have assumed that our survival functions are discrete, but this is not really necessary, as one may argue in the context of generalized maximum likelihood (see Johansen (1978)) that our estimates need place probability only on those timepoints at which observations occur.

3. REDUCTION OF THE PROBLEM.

Based on the notation in Section 2, the problem is to find survival functions $P_1,\cdots,P_N$ which maximize the likelihood

$$(3.1)\qquad \prod_{i=1}^{N}\left\{\prod_{r=1}^{\ell_{i0}} P(L_r^{(i,0)}) \prod_{j=1}^{m}\left\{[P_i(S_j-0)-P_i(S_j)]^{d_{ij}} \prod_{r=1}^{\ell_{ij}} P_i(L_r^{(i,j)})\right\}\right\},$$

subject to the constraints

$$(3.2)\qquad P_i(t) \geq P_{i+1}(t) \quad \forall t,\ \ i=1,\cdots,N-1.$$

For a given set of survival functions $P_1,\cdots,P_N$ satisfying (3.2), we note that the likelihood cannot be decreased and (3.2) cannot be violated if we replace $P_1(t)$ by a discrete $P_1'(t)$ which has possible jumps only at $S_1,\cdots,S_m$ and is such that $P_1'(S_j) = P_1(S_j)$. If we now replace $P_2(t)$ by $P_2'(t)$ defined to have possible jumps only as $S_1,\cdots,S_m$ and $P_2'(S_j) = P_2(S_j)$, the likelihood cannot decrease and (3.2) cannot be violated.

Continuing this reasoning, we see it will suffice to maximize the expression

$$\prod_{i=1}^{N}\prod_{j=1}^{m}[P_i(S_{j-1})-P_i(S_j)]^{d_{ij}}\ P_i(S_j)^{\ell_{ij}}$$

subject to $P_i(S_j) \geq P_{i+1}(S_j)$ $\forall j$, $i=1,\cdots,N-1$ among those survival functions which place probability only at the points $S_1,S_2,\cdots,S_m$.

(We note that maximum likelihood estimates need not be uniquely defined if the last observation from a population is a loss. We will avoid this ambiguity by requiring our maximum likelihood estimates of the survival functions to be as small as possible.) Equivalently, we wish to maximize

$$\prod_{i=1}^{N} \prod_{j=1}^{m} \left[1 - \frac{P_i(S_j)}{P_i(S_{j-1})}\right]^{d_{ij}} \left[\frac{P_i(S_{j-1})}{P_i(S_{j-2})} \cdots P_i(S_1)\right]^{d_{ij}} \left[\frac{P_i(S_j)}{P_i(S_{j-1})} \cdots P_i(S_1)\right]^{\ell_{ij}},$$

or letting $p'_{ij} = \frac{P_i(S_j)}{P_i(S_{j-1})}$, to maximize

$$\prod_{i=1}^{N} \prod_{j=1}^{m} (1 - p'_{ij})^{d_{ij}} \, p'^{\,\ell_{ij}}_{ij} \prod_{r<j} p'^{\,d_{ij}+\ell_{ij}}_{ir}$$

subject to $\prod_{r=1}^{j} p'_{ir} \geq \prod_{r=1}^{j} p'_{i+1,r}$, $j = 1,\cdots,m$; $i = 1,\cdots,N-1$.

Finally, recalling that $n_{ij} = \sum_{r=j}^{m} (d_{ir}+\ell_{ir})$, letting $p_{ij} = \ln p'_{ij}$, and considering the log of the likelihood, it will suffice to maximize

$$f(p_1,\cdots,p_N) = \sum_{i=1}^{N} \sum_{j=1}^{m} d_{ij} \ln(1-e^{p_{ij}}) + (n_{ij} - d_{ij})p_{ij} \tag{3.3}$$

subject to the constraints

$$\sum_{r=1}^{j} p_{ir} \geq \sum_{r=1}^{j} p_{i+1,r}, \quad 0 \geq p_{ij} \geq -\infty \tag{3.4}$$

$$\text{for } j = 1,\cdots,m; \quad i = 1,\cdots,N-1.$$

The problem has been reduced to maximizing a concave function subject to linear inequality constraints.

Since we are maximizing a bounded concave function over a closed convex region, there must exist a solution $\hat{p} = (\hat{p}_1,\cdots,\hat{p}_N)$ which satisfies the constraints in equation (3.4) and maximizes equation (3.3). If the active constraints (those where equality holds) of equation (3.4) needed for a solution $\hat{p}$ were known, the number of variables could be reduced by using certain of the expressions in (3.4) with equality holding. Then expression (3.3) could be maximized by setting the appropriate partial derivatives equal to zero, or by other means, and solving for the remaining independent variables. Of course, determining which constraints are the active ones is, in general, a very difficult problem. However, by noting that certain equality constraints must hold, and then maximizing equation (3.3) subject to an arbitrary fixed set of equality constraints in (3.4), the general form of the solution $\hat{p}$ can be determined.

Notice that the constraints $\sum_{\ell=1}^{a_1} p_{i\ell} = \sum_{\ell=1}^{a_1} p_{i+1,\ell}$, $\sum_{\ell=1}^{a_2} p_{i\ell} = \sum_{\ell=1}^{a_2} p_{i+1,\ell},\cdots,$ $\sum_{\ell=1}^{a_k} p_{i\ell} = \sum_{\ell=1}^{a_k} p_{i+1,\ell}$ can be written as $\sum_{\ell=1}^{a_1} p_{i\ell} = \sum_{\ell=1}^{a_1} p_{i+1,\ell}$, $\sum_{\ell=a_1+1}^{a_2} p_{i\ell} = \sum_{\ell=a_1+1}^{a_2} p_{i+1,\ell},\cdots,$ $\sum_{\ell=a_{k-1}+1}^{a_k} p_{i\ell} = \sum_{\ell=a_{k-1}+1}^{a_k} p_{i+1,\ell}$, so that an arbitrary p_{ij} need be present in at most two active constraints. Thus suppose p_{ij} is present in

$$p_{i+1,b} = \sum_{\ell=a}^{b} p_{i\ell} - \sum_{\ell=a}^{b-1} p_{i+1,\ell},$$

and

$$p_{i,s} = \sum_{\ell=r}^{s} p_{i-1,\ell} - \sum_{\ell=r}^{s-1} p_{i,\ell}, \quad a \le j \le b \quad \text{and} \quad r \le j \le s.$$

Also suppose that $d_{ij} > 0$, and no other parameter equals p_{ij}. Then, with appropriate substitution, the partial derivative with respect to p_{ij} of equation (3.3) set equal to zero yields

$$(3.5) \qquad -\frac{d_{ij}e^{p_{ij}}}{(1-e^{p_{ij}})} + n_{ij} - d_{ij} = h_{ij} - k_{ij}$$

where

$$k_{ij} = -\frac{d_{i+1,b}e^{p_{i+1,b}}}{(1-e^{p_{i+1,b}})} + (n_{i+1,b}-d_{i+1,b})$$

and

$$h_{ij} = -\frac{d_{is}e^{p_{is}}}{(1-e^{p_{is}})} + (n_{is}-d_{is}).$$

Of course it doesn't matter which variables we choose as the dependent variables. It follows that k_{ij} must have constant value for $a \le j \le b$, providing $d_{i+1,j} > 0$, and h_{ij} must have constant value for $r \le j \le s$ if $d_{ij} > 0$. Solving the equation for p_{ij} yields a solution of the form

$$(3.6) \qquad p^*_{ij} = \ln\left(\frac{n_{ij}-d_{ij}+k_{ij}-h_{ij}}{n_{ij}+k_{ij}-h_{ij}}\right).$$

Inspection of h_{ij} and k_{ij} will reveal that $h_{ij} = k_{i-1,j}$ if both d_{ij} and $d_{i-1,j}$ are positive. If $d_{ij} = 0$, that part of the objective function (3.3) involving p_{ij} is linear in p_{ij} with nonnegative slope.

Intuitively, p^*_{ij} should be as large as possible, and hence equal to zero unless our constraints will not allow this. This would happen for example if $d_{11} > 0$, but $d_{21} = d_{22} = 0$. Then our constraints would require that $p_{11} = p_{21}$ and $p_{12} = p_{22}$. We make these substitutions, and then solve by derivative methods. We will show later that these solutions are still of the form (3.6) for appropriate k_{ij}, and appropriate definitions of indeterminate forms. Once $d_{ij} > 0$, $p^*_{i\ell} = 0$ if $d_{i\ell} = 0$, $\ell > j$. Note that if $p^*_{i\ell} = 0$ and $d_{i\ell} = 0$, then $h_{i\ell}$ is indeterminate, and hence does not violate our claim of constant h_{ij} over $r \le j \le s$. In any event, p^*_{ij} can always be written in the form of (3.6) if indeterminate values are properly defined.

Since the true solution, $\hat{p}$, is given by p^* for <u>some</u> set of active constraints, $\hat{p}$ is necessarily of the form

$$\hat{p}_{1j} = \ln\left(\frac{n_{1j}-d_{1j}+k_{1j}}{n_{1j}+k_{1j}}\right)$$

(3.7) $$\hat{p}_{ij} = \ln\left(\frac{n_{ij}-d_{ij}+k_{ij}-k_{i-1,j}}{n_{ij}+k_{ij}-k_{i-1,j}}\right) \qquad 2 \le i \le N-1$$

$$\hat{p}_{Nj} = \ln\left(\frac{n_{Nj}-d_{Nj}-k_{N-1,j}}{n_{Nj}-k_{N-1,j}}\right)$$

for appropriate values of k_{ij} and appropriate definitions of indeterminate forms.

Now, the problem is to identify the k_{ij}'s. Heuristically, since the k_{ij}'s may be interpreted as playing the same role as the n_{ij}'s, the estimates are obtained by transferring unfailed items from one sample to the next stochastically larger sample, and then using the Kaplan-Meier (maximum likelihood) estimate for each survival function. It will then turn out that the k_{ij}'s will never be negative, which seems reasonable in light of our one-sided restrictions. Of course probability could be transferred from one population to several larger populations, but (3.7) indicates that we do not need to think of things this way.

Even if the active constraints were known, a large number of simultaneous nonlinear equations would have to be solved to find $\hat{p}$. In the following sections, the k_{ij}'s will be characterized and a method using this characterization will be given to estimate the N survival functions, avoiding the simultaneous nonlinear equations problem.

4. KUHN-TUCKER CHARACTERIZATION

The characterization of the k_{ij}'s requires some theory from convex analysis. The problem of estimating N survival functions subject to the stochastic orderings given by equation (3.2) may be written in terms of a particular ordinary convex programming problem. An ordinary convex programming problem is to find the vector p which minimizes a given convex function $f_0(p)$ subject to the constraints $f_j(p) \leq 0$, $j = 1,\cdots,n$ where each f_j is a convex function on $\mathbb{R}^m$. By letting $f_0(p) = -f(p)$ from equation (3.3), and letting $f_{ij}(p) = \sum_{\ell=1}^{j} p_{i+1,\ell} - \sum_{\ell=1}^{j} p_{i\ell}$, $i = 1,\cdots,N-1$; $j = 1,\cdots,m$, our problem is couched in the terms of an ordinary convex programming problem. We call $\lambda = (\lambda_1,\lambda_2,\cdots,\lambda_n)$ a Kuhn-Tucker vector if $\lambda_j \geq 0$ for $j = 1,\cdots,n$, and if the unrestricted infimum of $h(p) = f_0(p) + \lambda_1 f_1(p) + \cdots + \lambda_n f_n(p)$ is equal to the restricted infimum of $f_0(p)$. The following theorem from Rockafellar (1970) characterizes Kuhn Tucker vectors, and will be useful in characterizing the k_{ij}'s.

Theorem 4.1. Let $\hat{\lambda}$ and $\hat{p}$ be vectors in $\mathbb{R}^n$ and $\mathbb{R}^m$ respectively. In order that $\hat{\lambda}$ is a Kuhn-Tucker vector for our problem and $\hat{p}$ is an optimal solution, the following conditions are necessary and sufficient.

(4.1)

a. $\hat{\lambda}_j \geq 0$, $f_j(\hat{p}) \leq 0$, and $\hat{\lambda}_j f_j(\hat{p}) = 0$ for $j = 1,\cdots,n$,

b. $\underset{\sim}{0} \in [\partial f_0(\hat{p}) + \hat{\lambda}_1 \partial f_1(\hat{p}) + \cdots + \hat{\lambda}_n \partial f_n(\hat{p})]$

where $\partial f_j(p)$ is the set of all subgradients of f_j at $\hat{p}$.

Since the true solution and a Kuhn-Tucker vector must satisfy the subgradient equation in (4.1b), the general form of a Kuhn-Tucker vector can be found for our problem using the general form of the solution given in equation (3.7).

<u>Theorem 4.2</u>. If $\hat{p}_{ij}$ denotes the solution to the problem specified in equations (3.3) and (3.4), then a Kuhn-Tucker vector corresponding to the constraints $f_{ij} = \sum_{\ell=1}^{j} p_{i+1,\ell} - \sum_{\ell=1}^{j} p_{i\ell} \le 0$ is given by

$$\lambda_{ij} = \begin{cases} k_{ij} - k_{i,j+1}, & 1 \le j < m \\ k_{im}, & j = m \end{cases}$$

when the solution $\hat{p}$ is specified in the form given by (3.7).

<u>Proof</u>: In the ordinary convex program characterization of our problem,

$$f_0(p) = -\left\{ \sum_{i=1}^{N} \sum_{j=1}^{m} d_{ij} \ln(1-e^{p_{ij}}) + (n_{ij}-d_{ij})p_{ij} \right\}$$

which we want to minimize subject to the constraints

$$f_{ij}(p) = \sum_{\ell=1}^{j} p_{i+1,\ell} - \sum_{\ell=1}^{j} p_{i\ell} \le 0 \quad \text{for} \quad i = 1,\cdots,N-1;\ j = 1,\cdots,m.$$

Notice that $f_0(p)$ and $f_{ij}(p)$, $i = 1,\cdots,N-1$; $j = 1,\cdots,m$ are differentiable functions of $p_{i'j'}$ for i' and j' so that equation (4.1b) can be written in matrix notation. (Of course the n in Theorem 4.1 is now $m(N-1)$.) Equation (4.1b) then becomes $\underset{\sim}{0} = F_0 + F\lambda$, where F_0 is the $Nm \times 1$ vector of derivatives of $f_0(p)$ with respect to p_{ij}, λ is an

$(N-1)m \times 1$ Kuhn-Tucker vector and F is the $Nm \times (N-1)m$ matrix of partial derivatives of f_{ij} with respect to $p_{i',j'}$ and $\underset{\sim}{0}$ is an $Nm \times 1$ vector of zeros.

Equivalently, we must have $F\lambda = -F_0$, and since F is of full column rank which is less than the number of rows, any solution to our equation must be unique. We may express F as

$$\begin{pmatrix} -T & 0 & 0 & \cdots & 0 \\ T & -T & 0 & \cdots & \vdots \\ 0 & T & -T & \cdots & \\ \vdots & \vdots & & T & -T \\ 0 & 0 & \cdots\cdots & & T \end{pmatrix}$$

where $T^{m \times m}$ is an upper triangular matrix of ones. We note that F_0 has the form

$$\begin{bmatrix} -k_{11} \\ \vdots \\ -k_{1m} \\ \vdots \\ k_{i1} - k_{i+1,1} \\ \vdots \\ k_{im} - k_{i+1,m} \\ \vdots \\ k_{N-1,1} \\ \vdots \\ k_{N-1,m} \end{bmatrix} \quad \text{where } i = 1, \cdots, N-2.$$

It can be verified that a conditional inverse of F is given by

$$F^c = \begin{pmatrix} T^{-1} & 0 & 0 & \cdots & \\ T^{-1} & T^{-1} & 0 & \cdots & \\ T^{-1} & T^{-1} & T^{-1} & \cdots & \\ \vdots & \vdots & \vdots & & \\ T^{-1} & T^{-1} & T^{-1} & \cdots & \end{pmatrix}$$

where

$$T^{-1} = \begin{pmatrix} 1 & -1 & 0 & 0 & \cdots & 0 \\ 0 & 1 & -1 & 0 & \cdots & 0 \\ 0 & 0 & 1 & -1 & & \\ \vdots & \vdots & \vdots & \cdots & 1 & -1 \\ 0 & 0 & 0 & \cdots & 0 & 1 \end{pmatrix}$$

Careful calculation will verify that $\lambda = -F^c F_0$ is of the desired form and a solution to equation (4.1b).

Conditions (4.1a) must hold if the λ_{ij}'s are to form a Kuhn-Tucker vector. If $\lambda_{ij} \geq 0$, the k_{ij}'s occurring in equation (3.7) must be such that

(4.2) $$k_{i1} \geq k_{i2} \geq \cdots \geq k_{im} \geq 0 \quad \text{for all } i.$$

Conversely, if equation (4.2) holds, the λ_{ij} will be nonnegative.

The condition that $\lambda_i f_i(\hat{p}) = 0$ in Theorem 4.1, together with the monotonicity requirement given in equation (4.2) leads to a characterization for the solution provided certain indeterminate forms are properly defined. Thus we have the following theorem.

Theorem 4.3. A solution to the problem of maximizing $f(p)$ given in equation (3.3) under the constraints in equation (3.4) are given by the $\hat{p}_{ij}$'s described in equation (3.7) iff the k_{ij}'s are such that:

a) the $\hat{p}_{ij}$'s in (3.7) satisfy the constraints in (3.4) and $-\infty \le \hat{p}_{ij} \le 0$,

b) $k_{i1} \ge k_{i2} \ge \cdots \ge k_{im} \ge 0$ for $i = 1,2,\cdots,N-1$, and

c) whenever $k_{ij} > k_{i,j+1}$, $\sum_{\ell=1}^{j} \hat{p}_{i\ell} = \sum_{\ell=1}^{j} \hat{p}_{i+1,\ell}$

provided some indeterminate forms are appropriately defined.

Indeterminate forms occur when $d_{ij} = 0$ for $i_0 < i$ and $j \le j_0$ and $d_{i_0,j_0} > 0$. In this case,

$$p_{i_0,j_0} = p_{i_0+1,j_0} = \cdots = p_{N,j_0} = \ln\left[\frac{\sum_{i=i_0}^{N} n_{i,j_0} - d_{i_0,j_0} - k_{i_0-1,j_0}}{\sum_{i=i_0}^{N} n_{i,j_0} - k_{i_0-1,j_0}}\right]$$

as mentioned earlier. Notice that this is consistent with (3.7) where we take

$$k_{ij} = \sum_{\ell=i+1}^{N} n_{\ell j}\ , \quad i > i_0, j \le j_0$$

since this leads to indeterminate forms.

5. OBTAINING THE $\hat{p}_{ij}$

Even though Theorem 4.3 characterizes the solution to the problem, it does not provide any means of obtaining the solution in general. However, for the case $N = 2$, Dykstra (1982) has found closed form expressions for the $\hat{p}_{ij}$ as well as an efficient algorithm for calculating them. We will elaborate on this procedure, and then give an iterative procedure based only on this pairwise scheme which will converge to the general solution. This will give us a means of solving the general problem.

To solve the pairwise problem, one need first identify the integer j_0 such that $d_{2j} = 0$, $j < j_0$, but $d_{2,j_0} > 0$. Then

$$\hat{p}_{1j} = \hat{p}_{2j} = \ln\left(\frac{n_{1j} + n_{2j} - d_{1j}}{n_{1j} + n_{2j}}\right) \tag{5.1}$$

(which requires that $k_{1j} = n_{2j}$) for $j < j_0$. For $j_0 \le a \le b$, we let $k_{a,b}$ denote the solution to

$$\sum_{j=a}^{b} \ln\left(\frac{n_{1j} - d_{1j} + k}{n_{1j} + k}\right) = \sum_{j=a}^{b} \ln\left(\frac{n_{2j} - d_{2j} - k}{n_{2j} - k}\right)$$

if it exists positively and 0 otherwise. Then Dykstra has shown the $\hat{p}_{ij}$ which maximize (3.3) subject to the linear constraints $\sum_{i=1}^{j} p_{1j} \ge \sum_{i=1}^{j} p_{2j}$ are of the form

$$\hat{p}_{1j} = \ln\left(\frac{n_{1j} - d_{1j} + \hat{k}_{1j}}{n_{1j} + \hat{k}_{1j}}\right); \quad \hat{p}_{2j} = \ln\left(\frac{n_{2j} - d_{2j} - \hat{k}_{1j}}{n_{2j} - \hat{k}_{1j}}\right) \tag{5.2}$$

where $\hat{k}_{1j} = \min_{a \le j} \max_{j \le b} k_{a,b}$ for $j \ge j_0$. The restricted mle's of $P_1(t)$ and $P_2(t)$ are then given by

$$\hat{P}_i(t) = \exp\left[\sum_{j;S_j \le t} \hat{p}_{ij}\right], \quad i = 1,2. \tag{5.3}$$

We shall take $\hat{P}_i(t)$ to be as small as possible subject to the order restrictions so as to ensure uniqueness of the estimates. Using the fact that $k_{11} \ge k_{12} \ge \cdots \ge k_{1m}$, Dykstra has derived an algorithm which can be used to compute the mle of p_{1j} and p_{2j} for $j = 1,\cdots,m$. This algorithm is given below:

Pairwise Algorithm

Algorithm for two survival functions $P_1(t) \ge P_2(t)$:

1. Define $\hat{p}_{ij}$ (and k_{1j}) as in (5.1) for $j < j_0$.

2. Find the largest $j_1 \ge j_0$ such that the $k_{1j_1} > 0$ which solves

$$\sum_{j=j_0}^{j_1} \ln\left(\frac{n_{1j} - d_{1j} + k}{n_{1j} + k}\right) = \sum_{j=j_0}^{j_1} \ln\left(\frac{n_{2j} - d_{2j} - k}{n_{2j} - k}\right)$$

is maximized. Then let $k_{1j} = k_{1j_1}$ for $j_0 \le j \le j_1$.

3. Find the largest $j_2 > j_1$ such that the $k_{1j_2} > 0$ which solves

$$\sum_{j=j_1+1}^{j_2} \ln\left(\frac{n_{1j} - d_{1j} + k}{n_{1j} + k}\right) = \sum_{j=j_1+1}^{j_2} \ln\left(\frac{n_{2j} - d_{2j} - k}{n_{2j} - k}\right)$$

is maximized. Let $k_{1j} = k_{1j_2}$ for $j_1 < j \le j_2$.

4. Continue until either $j_h = m$ or no such positive k_{1j_h} exists, in which case let $k_{1j} = 0$ for $j > j_{h-1}$. Then $\hat{p}_{ij}$ and $\hat{P}_i(t)$ are given as in (5.2) and (5.3) respectively.

The N sample problem can be solved using an iterative procedure based upon the pairwise algorithm given previously. The pairwise method is used to massage (readjust) the data until an equilibrium point is reached. Letting $k_{ij}^{(\ell)}$ be the estimate of k_{ij} found during the ℓ^{th} iteration of the algorithm, the N sample algorithm is given as follows:

1. Find the $k_{1,j}^{(1)}$'s corresponding to $P_1 \geq P_2$ using the pairwise algorithm given previously.

2. Incorporate $k_{1,j}^{(1)}$ into $n_{1,j}$ and $n_{2,j}$ by replacing $n_{1,j}$ by $n_{1,j} + k_{1,j}^{(1)}$ and $n_{2,j}$ by $n_{2,j} - k_{1,j}^{(1)}$.

3. Using the adjusted data, find the $k_{2,j}^{(1)}$'s corresponding to $P_2 \geq P_3$ using the pairwise algorithm.

4. Replace $n_{2,j} - k_{1,j}^{(1)}$ by $n_{2,j} + k_{2,j}^{(1)} - k_{1,j}^{(1)}$ and $n_{3,j}$ by $n_{3,j} - k_{2,j}^{(1)}$.

5. Continue down the chain of survival functions until the $N\text{-}1^{th}$ and N^{th} samples have been compared, and $n_{N-1,j}$ has been replaced by $n_{N-1,j} - k_{N-2,j}^{(1)} + k_{N-1,j}^{(1)}$ and $n_{N,j}$ has been replaced by $n_{N,j} - k_{N-1,j}^{(1)}$.

6. The procedure starts again at the top of the chain. After setting $k_{1,j}^{(1)} = 0$ for $j = 1, \cdots, m$, find the $k_{1,j}^{(2)}$ corresponding to $P_1 \geq P_2$ using the pairwise algorithm.

7. Incorporate $k_{1,j}^{(2)}$ into the data by replacing $n_{1,j}$ by $n_{1,j} + k_{1,j}^{(2)}$ and $n_{2,j} + k_{2,j}^{(1)}$ by $n_{2,j} + k_{2,j}^{(1)} - k_{1,j}^{(2)}$.

8. After setting $k_{2,j}^{(1)} = 0$ for $j = 1, \cdots, m$, use the pairwise algorithm to find $k_{2,j}^{(2)}$ for $P_2 \geq P_3$ and incorporate $k_{2,j}^{(2)}$ by replacing

$n_{2,j} - k_{1,j}^{(2)}$ by $n_{2,j} + k_{2,j}^{(2)} - k_{1,j}^{(2)}$ and $n_{3,j} + k_{3,j}^{(1)}$ by $n_{3,j} + k_{3,j}^{(1)} - k_{2,j}^{(2)}$.

9. Continue down the chain, taking out the effect of the comparison ($k_{ij}^{(1)}$) in the previous iteration, recomparing $P_i \geq P_{i+1}$, and then reincorporating the new $k_{ij}^{(2)}$'s.

10. When the bottom of the chain is reached, start with this procedure again at the top of the chain and continue until achieving convergence.

The estimated $\hat{p}_{ij}$'s are then obtained from (3.7) and the latter part of Theorem 4.3 with the $k_{ij}^{(\ell)}$ obtained above entered in. We will let $\hat{p}_{ij}^{(\ell)}$ indicate (3.7) with the $k_{ij}^{(\ell)}$'s entered.

<u>Theorem 5.1</u>. The procedure discussed above must yield values of $\hat{p}_{ij}^{(\ell)}$ which converge for every i and j as $\ell \to \infty$. Moreover, these limiting values solve the problem of maximizing $f(p)$ subject to the constraints $\sum_{\ell=1}^{j} p_{i\ell} \geq \sum_{\ell=1}^{j} p_{i+1,\ell}$ *for* $j = 1, \cdots, m$; $i = 1, \cdots, N-1$.

<u>Proof</u>: Consider the first step of the second cycle. We obtain $k_{1j}^{(2)}$ by using the pairwise algorithm for $P_1 \geq P_2$ with the data n_{1j}, and $n_{2j} + k_{2j}^{(1)}$ in place of n_{1j} and n_{2j}. We need to consider two cases:

1. If $d_{2\ell} = 0$ for $\ell \leq j$, then $k_{1j}^{(2)} = n_{2j} + k_{2j}^{(1)} \geq n_{2j} = k_{1j}^{(1)}$.

2. Otherwise $k_{1j}^{(2)} = \min\limits_{a \leq j} \max\limits_{j \leq b} k'_{a,b}$ where $k'_{a,b}$ is positive and solves

$$\sum_{j=a}^{b} \ln\left(\frac{n_{1j} - d_{1j} + k}{n_{1j} + k}\right) = \sum_{j=a}^{b} \ln\left(\frac{n_{2j} + k_{2j}^{(1)} - d_{2j} - k}{n_{2j} + k_{2j}^{(1)} - k}\right)$$

or is zero.

If $k_{a,b}$ is positive and solves

$$\sum_{j=a}^{b} \ln\left(\frac{n_{1j} - d_{1j} + k}{n_{1j} + k}\right) = \sum_{j=a}^{b} \ln\left(\frac{n_{2j} - d_{2j} - k}{n_{2j} - k}\right),$$

it easily follows that $k'_{a,b} \geq k_{a,b}$ for all a,b, and hence

$$k_{1j}^{(2)} \geq k_{1j}^{(1)}.$$

Similar arguments suffice for other i, and we may conclude that $k_{ij}^{(\ell)}$ is nondecreasing in ℓ for all i,j. Since the $k_{ij}^{(\ell)}$ are uniformly bounded (say by $\sum_{i=1}^{N} n_{i1}$), we know there exists k_{ij} such that $k_{ij}^{(\ell)} \nearrow k_{ij}$. Finally, noting that the $\hat{p}_{ij}$ in (3.7) are continuous functions of the k_{ij}, and that the $k_{ij}^{(\ell)}$ correspond to solutions of the pairwise problems, we can argue that the $\hat{p}_{ij}$ defined by (3.7) for the limiting values k_{ij} satisfy the conditions of Theorem 4.3, and hence solve the general problem.

We mention again the appealing form of the estimators. They are still of the Kaplan-Meier form, where, heuristically, unfailed items from a population are transferred to the next stochastically larger population.

6. EXAMPLE

This example involves a large clinical trial carried out by the Radiation Therapy Oncology Group cited in Kalbfleisch and Prentice (1980). The analysis was done on only a small part of the data, and females were deleted to make the data more homogeneous. Patients diagnosed with squamous carcinoma of the oropharynx were classified by the degree to which the regional lymph nodes were affected by this disease.

We let P_1 be the survival function corresponding to those patients for whom the disease had no effect on the lymph nodes. Correspondingly, we let P_2, P_3, and P_4 be the survival functions of patients with increased effects of the disease on the lymph nodes. The data for each survival function is given in Table 1.

Because of the nature of the disease, one would certainly expect a linear ordering with respect to lymphatic involvement. Thus an ordering of the form $P_1 \overset{st}{\geq} P_2 \overset{st}{\geq} P_3 \overset{st}{\geq} P_4$ seems inherently reasonable.

The unrestricted mle's (Kaplan-Meier) for these survival functions are given in Table 3. Notice that with respect to the expected orderings, there are reversals so that estimates requiring these orderings will be different. The algorithm given in Section 5 was applied to the problem. The k_{ij} values found in the first two iterations, in the order in which they were found, along with the essentially limiting values obtained after 20 cycles are given in Table 2. (The procedure used here actually worked pairwise from bottom to top rather than from top to bottom as indicated in the paper. Of course, the limiting values will be identical.) The values of these $k_{ij}^{(\ell)}$ indicate how much "smoothing" is occurring between populations.

The mle's subject to the stochastic ordering $P_1 \overset{st}{\geq} P_2 \overset{st}{\geq} P_3 \overset{st}{\geq} P_4$, obtained via our algorithm are displayed in Table 4. Note that the stochastic ordering requirement has brought substantial change in our estimates.

TABLE 1

Survival Times in Days of Patients with Squamous Carcinoma in the Oropharynx with Various Degrees of Lymph Node Deterioration (+ denotes censored observation).

Degrees of deterioration of lymph nodes.

i = 1	i = 2	i = 3	i = 4
167	216	105	94
238	324	222	99
276+	338	279	112
296	347	395	127
324	599	465	134
351	763	546	147
372	929	915	192
374	1086+	918	219
404	1092	1058+	255
445+	1317+	1455+	262
541	1609+	1644+	274
560			293
943			307
998+			327
1234+			334
1460+			363
1823+			407
			413+
			459
			517
			532
			544
			672
			696
			800
			914
			1312+
			1446+
			1472+

(The degree of deterioration (i) equals N-stage tumor classification in Kalbfleisch and Prentice (1980) plus one.)

TABLE 2

Values of the $k_{ij}^{(\ell)}$ obtained for survival data in Table 1.

First cycle:

$k_{3j}^{(1)} = 2.333$	$j \le 3$	$T \le 105$
0	$j > 3$	$T > 105$
$k_{2j}^{(1)} = 1.853$	$j \le 29$	$T \le 374$
1.205	$29 < j \le 53$	$374 < T \le 1609$
0	$j > 53$	$T > 1609$
$k_{1j}^{(1)} = 12.853$	$j \le 9$	$T \le 192$
4.380	$9 < j \le 40$	$192 < T \le 560$
0	$j > 40$	$T > 560$

Second cycle:

$k_{3j}^{(2)} = 3.569$	$j \le 3$	$T \le 105$
0	$j > 3$	$T > 105$
$k_{2j}^{(2)} = 5.481$	$j \le 11$	$T \le 219$
3.752	$11 < j \le 29$	$219 < T \le 374$
1.205	$29 < j \le 53$	$374 < T \le 1609$
0	$j > 53$	$T > 1609$
$k_{1j}^{(2)} = 12.853$	$j \le 9$	$T \le 192$
5.847	$9 < j \le 40$	$192 < T \le 560$
0	$j > 40$	$T > 560$

⋮

Twentieth cycle:

$k_{3j}^{(20)} = 10.525$	$j \le 3$	$T \le 105$
1.438	$3 < j \le 17$	$105 < T \le 279$
0	$j > 17$	$T > 279$
$k_{2j}^{(20)} = 12.290$	$j \le 11$	$T \le 219$
5.763	$11 < j \le 29$	$219 < T \le 374$
1.205	$29 < j \le 53$	$374 < T \le 1609$
0	$j > 53$	$T > 1609$
$k_{1j}^{(20)} = 12.853$	$j \le 9$	$T \le 192$
10.371	$9 < j \le 20$	$192 < T \le 307$
7.253	$20 < j \le 40$	$307 < T \le 560$
0	$j > 40$	$T > 560$

TABLE 3
Kaplan-Meier MLE's of survival functions from data

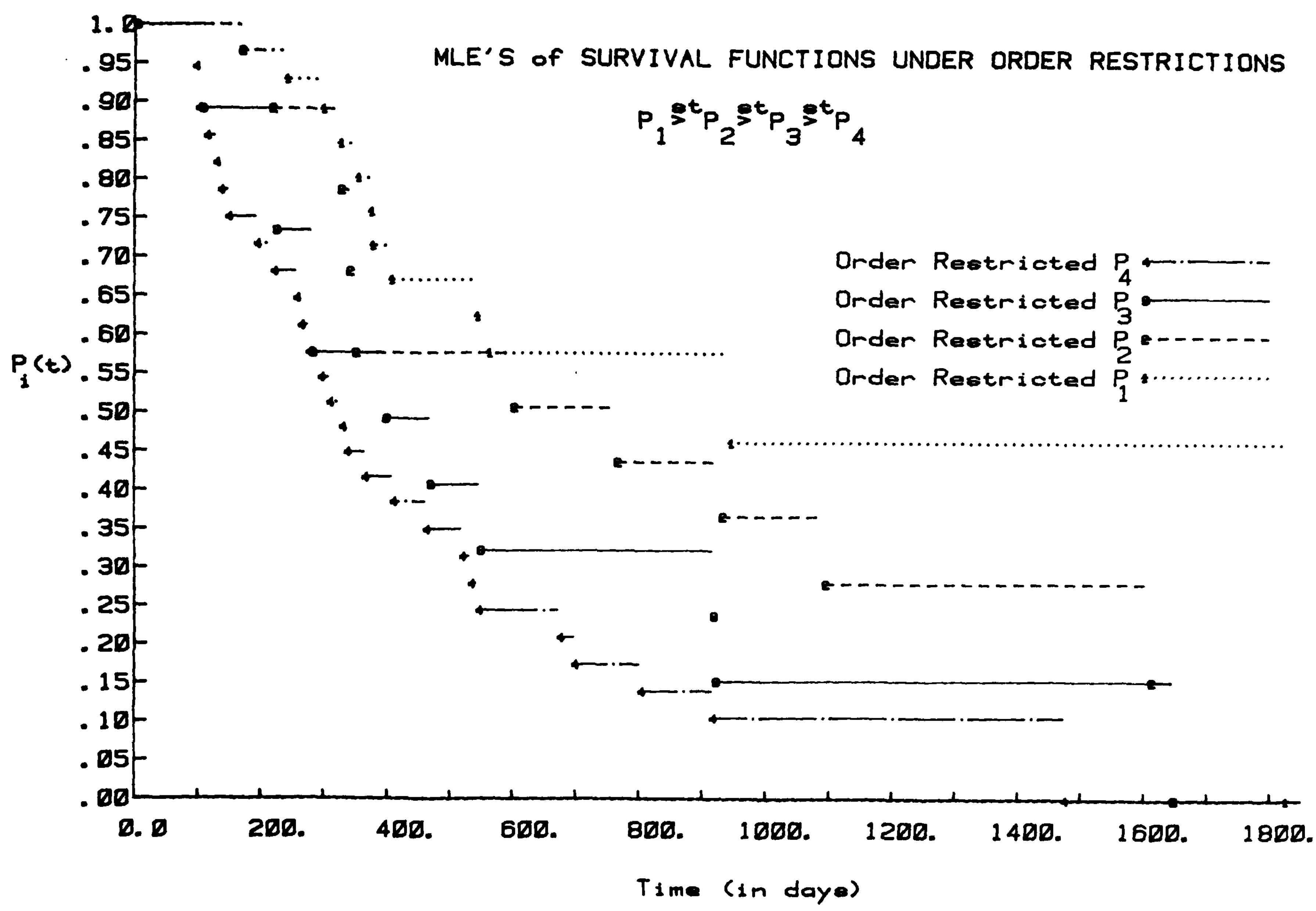
Index	Time	P_1	P_2	P_3	P_4
0	0.0	1.0000	1.0000	1.0000	1.0000
1	94	1.0000	1.0000	1.0000	.9655
2	99	1.0000	1.0000	1.0000	.9310
3	105	1.0000	1.0000	.9091	.9310
4	112	1.0000	1.0000	.9091	.8966
5	127	1.0000	1.0000	.9091	.8621
6	134	1.0000	1.0000	.9091	.8276
7	147	1.0000	1.0000	.9091	.7931
8	167	.9412	1.0000	.9091	.7931
9	192	.9412	1.0000	.9091	.7586
10	216	.9412	.9091	.9091	.7586
11	219	.9412	.9091	.9091	.7241
12	222	.9412	.9091	.8182	.7241
13	238	.8824	.9091	.8182	.7241
14	255	.8824	.9091	.8182	.6897
15	262	.8824	.9091	.8182	.6552
16	274	.8824	.9091	.8182	.6207
17	279	.8824	.9091	.7273	.6207
18	293	.8824	.9091	.7273	.5862
19	296	.8193	.9091	.7273	.5862
20	307	.8193	.9091	.7273	.5517
21	324	.7563	.8182	.7273	.5517
22	327	.7563	.8182	.7273	.5172
23	334	.7563	.8182	.7273	.4828
24	338	.7563	.7272	.7273	.4828
25	347	.7563	.6364	.7273	.4828
26	351	.6933	.6364	.7273	.4828
27	363	.6933	.6364	.7273	.4483
28	372	.6303	.6364	.7273	.4483
29	374	.5672	.6364	.7273	.4483
30	395	.5672	.6364	.6364	.4483
31	404	.5042	.6364	.6364	.4483
32	407	.5042	.6364	.6364	.4138
33	459	.5042	.6364	.6364	.3762
34	465	.5042	.6364	.5455	.3762
35	517	.5042	.6364	.5455	.3386
36	532	.5042	.6364	.5455	.3009
37	541	.4322	.6364	.5455	.3009
38	544	.4322	.6364	.5455	.2633
39	546	.4322	.6364	.4546	.2633
40	560	.3601	.6364	.4546	.2633
41	599	.3601	.5455	.4546	.2633
42	672	.3601	.5455	.4546	.2257
43	696	.3601	.5455	.4546	.1881
44	763	.3601	.4546	.4546	.1881
45	800	.3601	.4546	.4546	.1505
46	914	.3601	.4546	.4546	.1129
47	915	.3601	.4546	.3636	.1129
48	918	.3601	.4546	.2727	.1129
49	929	.3601	.3636	.2727	.1129
50	943	.2881	.3636	.2727	.1129
51	1092	.2881	.2424	.2727	.1129
52	1472	.2881	.2424	.2727	.0000
53	1609	.2881	.0000	.2727	.0000
54	1644	.2881	.0000	.0000	.0000
55	1823	.0000	.0000	.0000	.0000

TABLE 4

MLE's of survival functions under order restrictions from data in Table 1.

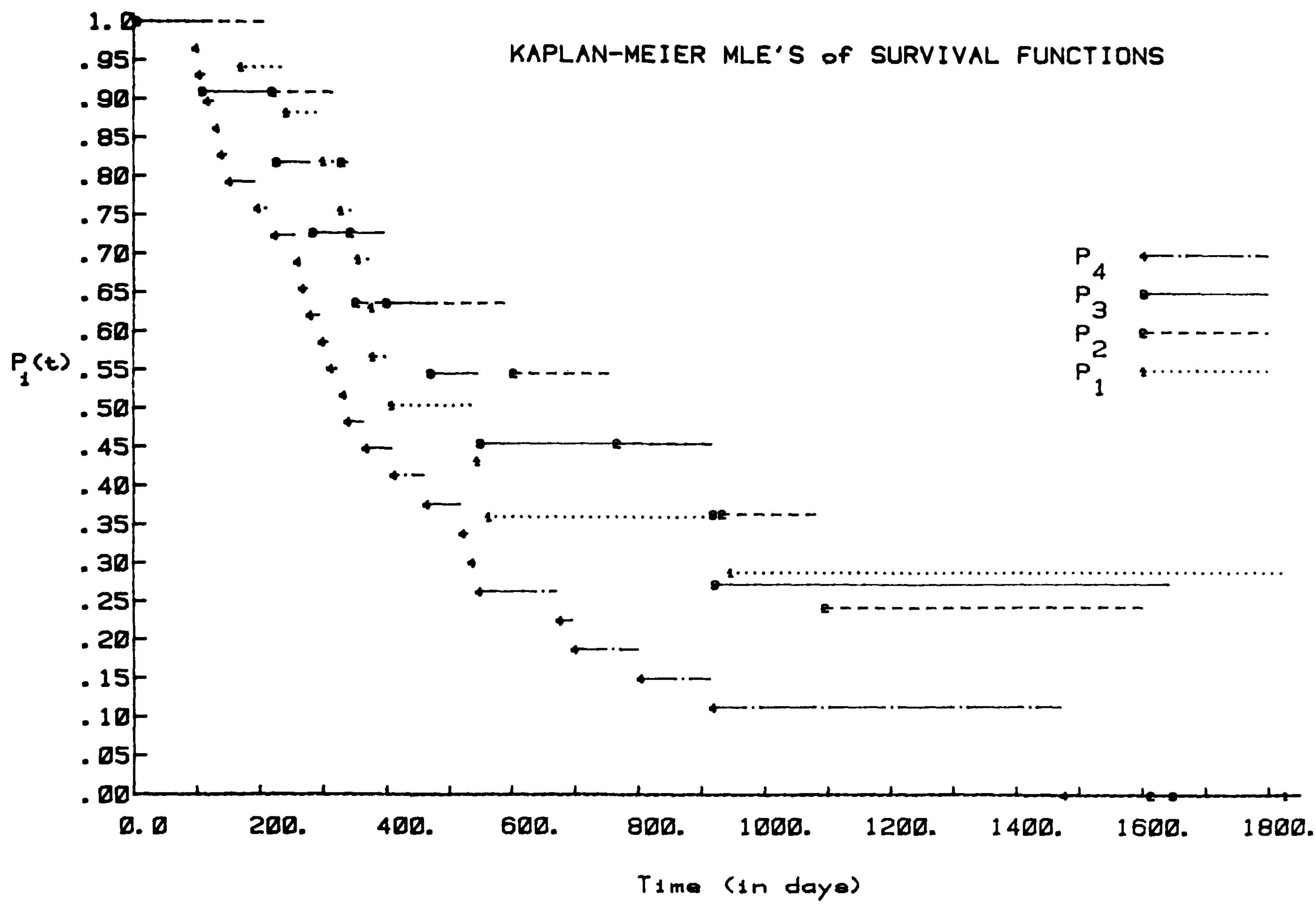
Index	Time	P_1	P_2	P_3	P_4
0	0.0	1.0000	1.0000	1.0000	1.0000
1	94	1.0000	1.0000	1.0000	.9459
2	99	1.0000	1.0000	1.0000	.8918
3	105	1.0000	1.0000	.8917	.8918
4	112	1.0000	1.0000	.8917	.8569
5	127	1.0000	1.0000	.8917	.8220
6	134	1.0000	1.0000	.8917	.7871
7	147	1.0000	1.0000	.8917	.7522
8	167	.9665	.9665	.8917	.7522
9	192	.9665	.9665	.8917	.7173
10	216	.9665	.8917	.8917	.7173
11	219	.9665	.8917	.8917	.6824
12	222	.9665	.8917	.7346	.6824
13	238	.9299	.8917	.7346	.6824
14	255	.9299	.8917	.7346	.6476
15	262	.9299	.8917	.7346	.6127
16	274	.9299	.8917	.7346	.5778
17	279	.9299	.8917	.5775	.5778
18	293	.9299	.8917	.5775	.5457
19	296	.8917	.8917	.5775	.5457
20	307	.8917	.8917	.5775	.5136
21	324	.8477	.7869	.5775	.5136
22	327	.8477	.7869	.5775	.4815
23	334	.8477	.7869	.5775	.4494
24	338	.8477	.6821	.5775	.4494
25	347	.8477	.5773	.5775	.4494
26	351	.8036	.5773	.5775	.4494
27	363	.8036	.5773	.5775	.4173
28	372	.7596	.5773	.5775	.4173
29	374	.7156	.5773	.5775	.4173
30	395	.7156	.5773	.4925	.4173
31	404	.6716	.5773	.4925	.4173
32	407	.6716	.5773	.4925	.3852
33	459	.6716	.5773	.4925	.3502
34	465	.6716	.5773	.4075	.3502
35	517	.6716	.5773	.4075	.3152
36	532	.6716	.5773	.4075	.2801
37	541	.6245	.5773	.4075	.2801
38	544	.6245	.5773	.4075	.2451
39	546	.6245	.5773	.3225	.2451
40	560	.5773	.5773	.3225	.2451
41	599	.5773	.5070	.3225	.2451
42	672	.5773	.5070	.3225	.2101
43	696	.5773	.5070	.3225	.1751
44	763	.5773	.4366	.3225	.1751
45	800	.5773	.4366	.3225	.1401
46	914	.5773	.4366	.3225	.1051
47	915	.5773	.4366	.2375	.1051
48	918	.5773	.4366	.1526	.1051
49	929	.5773	.3662	.1526	.1051
50	943	.4619	.3662	.1526	.1051
51	1092	.4619	.2791	.1526	.1051
52	1472	.4619	.2791	.1526	.0000
53	1609	.4619	.1525	.1526	.0000
54	1644	.4619	.0000	.0000	.0000
55	1823	.0000	.0000	.0000	.0000

FIGURE 2.



MLE'S of SURVIVAL FUNCTIONS UNDER ORDER RESTRICTIONS
$P_1 \overset{st}{\geq} P_2 \overset{st}{\geq} P_3 \overset{st}{\geq} P_4$
Order Restricted P_4
Order Restricted P_3
Order Restricted P_2
Order Restricted P_1
$P_i(t)$
1.0
.95
.90
.85
.80
.75
.70
.65
.60
.55
.50
.45
.40
.35
.30
.25
.20
.15
.10
.05
.00
0.0
200.
400.
600.
800.
1000.
1200.
1400.
1600.
1800.
Time (in days)

FIGURE 1.



KAPLAN-MEIER MLE'S of SURVIVAL FUNCTIONS
$P_i(t)$
1.0
.95
.90
.85
.80
.75
.70
.65
.60
.55
.50
.45
.40
.35
.30
.25
.20
.15
.10
.05
.00
0.0
200.
400.
600.
800.
1000.
1200.
1400.
1600.
1800.
Time (in days)
P_4
P_3
P_2
P_1

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Very often, populations exist that, logically, should satisfy linear stochastic ordering requirements. For example if a mechanical device is improved through N stages, the corresponding survival functions should be linearly stochastically ordered. Nevertheless, estimates may not reflect this stochastic ordering because of the inherent variability of the observations.

Here we characterize the maximum likelihood estimates of the survival functions subject to linear stochastic ordering requirements. We show our estimates may be expressed in terms of the well-known Kaplan-Meier product limit

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estimates. We also give an iterative algorithm which we show must converge to the correct solution that depends only upon solving the pairwise problem.

Finally we consider an example concerning survival times for people with squamous carcinoma in the oropharynx when classified by degree of lymph node deterioration at time of discovery.

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